CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207981Orig1s009

Trade Name:	LONSURF
Generic or Proper Name:	trifluridine and tipiracil
Sponsor:	Taiho Oncology, Inc.
Approval Date:	January 1, 2020
Indication:	Lonsurf is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with: • metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. • metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 207981/S-009

SUPPLEMENT APPROVAL/
FULLFILMENT OF POSTMARKETING REQUIRMENT

Taiho Oncology, Inc.
Attention: Alpesh Patel
Director, Regulatory Affairs
101 Carnegie Center, Suite 101
Princeton, NJ 08540

Dear Mr. Patel:

Please refer to your supplemental new drug application (sNDA) dated June 24, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) Lonsurf (trifluridine and tipiracil), tablets, 15 mg, trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil.

This Prior Approval new supplemental drug application provides for updates to the Dosage and Administration, Recommended Dosage for Renal Impairment subsection (2.3), Use in Specific Populations, Renal Impairment subsection (8.6), and the Clinical Pharmacology, Pharmacokinetics subsection (12.3) of the package insert to incorporate data from the study used to fulfill PMR 2963-2.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]
The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated June 21, 2019, containing the final report for the following postmarketing requirement listed in the September 22, 2015, approval letter.

PMR 2963-2

> Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

We have reviewed your submission and conclude that the above requirement was fulfilled.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This completes all of your postmarketing requirements acknowledged in our September 22, 2015, letter.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Jeff Summers, M.D.
Deputy Director for Safety
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEFFERY L SUMMERS
01/01/2020 05:30:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s009

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LONSURF safely and effectively. See full prescribing information for LONSURF.

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1.2)	2/2019
Recommended Dosage (2.1)	2/2019
Warnings and Precaution (5.1)	2/2019

INDICATIONS AND USAGE

LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with:

- metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. (1.1)
- metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy. (1.2)

DOSAGE AND ADMINISTRATION

- Recommended Dosage: 35 mg/m^2/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil (3)
- 20 mg trifluridine/8.19 mg tipiracil (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Severe Myelosuppression: Obtain complete blood counts prior to and on Day 15 of each cycle. Withhold and resume at next lower LONSURF dosage as recommended. (2.1, 5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions or laboratory abnormalities (≥10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taiho Oncology, Inc. at 1-844-878-2446 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older. (8.5)
- Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe hepatic impairment. (8.7)
- Renal Impairment: Reduce LONSURF dose in patients with severe renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12 /2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

1.2 Metastatic Gastric Cancer

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of LONSURF is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. Round dose to the nearest 5 mg increment.

Instruct patients to swallow LONSURF tablets whole.

Instruct patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Table 1 shows the calculated initial daily dose based on body surface area (BSA).

Table 1 Recommended Dosage According to Body Surface Area (BSA)

BSA (m2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15mg	20mg
< 1.07	70	35	1	1
1.07 - 1.22	80	40	0	2
1.23 - 1.37	90	45	3	0
1.38 - 1.52	100	50	2	1
1.53 - 1.68	110	55	1	2
1.69 - 1.83	120	60	0	3
1.84 - 1.98	130	65	3	1
1.99 - 2.14	140	70	2	2
2.15 - 2.29	150	75	1	3
≥2.30	160	80	0	4

2.2 Dosage Modifications for Adverse Reactions

Obtain complete blood cell counts prior to and on Day 15 of each cycle *[see Warnings and Precautions (5.1)]*.

Do not initiate the cycle of LONSURF until:

- Absolute neutrophil count (ANC) greater than or equal to 1,500/mm^3 or febrile neutropenia is resolved
- Platelets greater than or equal to 75,000/mm^3
- Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1

Within a treatment cycle, withhold LONSURF for any of the following:

- Absolute neutrophil count (ANC) less than 500/mm^3 or febrile neutropenia
- Platelets less than 50,000/mm^3
- Grade 3 or 4 non-hematologic adverse reaction

After recovery, resume LONSURF after reducing the dose by 5 mg/m^2/dose from the previous dose, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm^3) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm^3) that results in more than 1 week delay in start of next cycle
- Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

A maximum of 3 dose reductions are permitted. Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m^2 orally twice daily. Do not escalate LONSURF dosage after it has been reduced.

2.3 Recommended Dosage for Renal Impairment

Severe Renal Impairment

In patients with severe renal impairment [creatinine clearance (CLcr) of 15 to 29 mL/min as determined by the Cockcroft-Gault formula], the recommended dosage is 20 mg/m^2 (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle (Table 2) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Reduce dose to 15 mg/m^2 twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily (Table 2). Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 15 mg/m^2 twice daily.

Table 2 Recommended Dosage for Severe Renal Impairment According to BSA

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15mg	20mg
For a dose of 20 mg/m^2 twice daily:				
< 1.14	40	20	0	1
1.14 – 1.34	50	25*	2 in the evening*	1 in the morning*
1.35 – 1.59	60	30	2	0
1.60 – 1.94	70	35	1	1
1.95 – 2.09	80	40	0	2
2.10 – 2.34	90	45	3	0
≥ 2.35	100	50	2	1
For a dose of 15 mg/m^2 twice daily:				
< 1.15	30	15	1	0
1.15 – 1.49	40	20	0	1
1.50 – 1.84	50	25*	2 in the evening*	1 in the morning*
1.85 – 2.09	60	30	2	0
2.10 – 2.34	70	35	1	1
≥ 2.35	80	40	0	2

* For a total daily dose of 50 mg, instruct patients to take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil: white, biconvex, round, film-coated, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink.
- 20 mg trifluridine/8.19 mg tipiracil: pale red, biconvex, round, film-coated, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in gray ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

In the 868 patients who received LONSURF in RECOURSE and TAGS, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection/sepsis and four other patients (0.5%) died due to septic shock. A total of 12% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage *[*see *Dosage and Administration (2.2)]*.

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m^2 twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with LONSURF and for at least 6 months after the final dose *[*see *Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe Myelosuppression *[*see *Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS section and below reflect exposure to LONSURF at the recommended dose in 533 patients with metastatic colorectal cancer in RECOURSE and 335 patients with metastatic gastric cancer in TAGS. Among the 868 patients who received LONSURF, 11% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities (≥10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia.

Metastatic Colorectal Cancer

The safety of LONSURF was evaluated in RECOURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer *[see Clinical Studies (14.1)]*. Patients received LONSURF 35 mg/m^2/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. In RECOURSE, 12% of patients received LONSURF for more than 6 months and 1% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years; 61% male; 57% White, 35% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In RECOURSE, 3.6% of patients discontinued LONSURF for an adverse reaction and 14% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Tables 3 and 4 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in RECOURSE.

Table 3 Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in RECOURSE

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
General				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1	14	<1
Gastrointestinal				
Nausea	48	2	24	1
Diarrhea	32	3	12	<1
Vomiting	28	2	14	<1
Abdominal pain	21	2	18	4
Stomatitis	8	<1	6	0
Metabolism and nutrition				
Decreased appetite	39	4	29	5
Infections†	27	6	16	5
Nervous system				
Dysgeusia	7	0	2	0
Skin and subcutaneous tissue				
Alopecia	7	0	1	0

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology
†Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.

Table 4 Laboratory Abnormalities in RECOURSE

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematologic				
Anemia†	77	18	33	3
Neutropenia	67	38	1	0
Thrombocytopenia	42	5	8	<1

* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post-baseline samples, which may be <533 (LONSURF) or 265 (placebo)
† One Grade 4 anemia adverse reaction based on clinical criteria was reported

In RECOURSE, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

Metastatic Gastric Cancer

The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), double-blind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease *[see Clinical Studies (14.2)]*. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Patients received LONSURF 35 mg/m^2/dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. In TAGS, 10% of patients received LONSURF for more than 6 months and 0.9% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years (24 to 89 years); 73% male; 70% White, 16% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were neutropenia, anemia, nausea, decreased appetite, thrombocytopenia, vomiting, and diarrhea.

In TAGS, 13% of patients discontinued LONSURF for an adverse reaction and 11% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, and diarrhea.

Tables 5 and 6 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in TAGS.

Table 5 Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in TAGS

Adverse Reactions	LONSURF (N=335)		Placebo (N=168)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
Gastrointestinal				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
Metabolism and nutrition				
Decreased appetite	34	9	31	7
Infections†	23	5	16	5

*No Grade 4 definition for nausea or fatigue in NCI CTCAE, version 4.03.
†Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.

Table 6 Laboratory Abnormalities in TAGS

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematologic				
Neutropenia	66	38	4	0
Anemia†	63	19	38	7
Thrombocytopenia	34	6	9	0

* Worst Grade at least one Grade higher than baseline, with percent based on number of patients with post-baseline samples which may be <335 (LONSURF) or 168 (placebo)
† Anemia: No Grade 4 definition in CTCAE, v4.03

In TAGS, pulmonary emboli occurred more frequently in LONSURF-treated patients (3.1%) compared to 1.8% for patients on placebo.

Additional Clinical Experience

Interstitial lung disease was reported in 15 (0.2%) patients, 3 of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action *[see Clinical Pharmacology (12.2)]*, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to human exposures at the recommended clinical dose *(see Data)*. There are no available data on LONSURF use in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses ≥50 mg/kg (approximately 0.33 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of trifluridine, tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in

maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifluridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LONSURF *[see Use in Specific Populations (8.1)]*.

Contraception

LONSURF can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of LONSURF in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses ≥ 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

In RECOURSE and TAGS, 868 patients received LONSURF; 45% were 65 years of age or over, while 10% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients. Patients 65 years of age or older who received LONSURF had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs. 32%), Grade 3 anemia (22% vs. 16%), and Grade 3 or 4 thrombocytopenia (7% vs. 4%).

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) *[see Dosage and Administration (2.3)]*. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

8.7 Hepatic Impairment

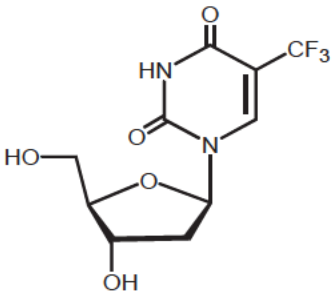
No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

LONSURF contains trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5.

Trifluridine

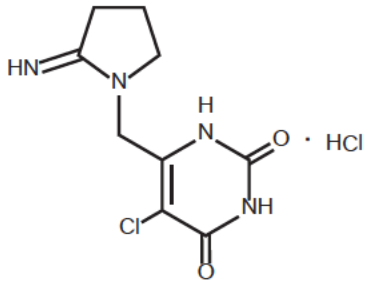
Trifluridine, a nucleoside metabolic inhibitor, is described chemically as 2'-deoxy-5-(trifluoromethyl) uridine and has the following structural formula:



Trifluridine has a molecular formula $C_{10}H_{11}F_3N_2O_5$ and a molecular weight of 296.20. Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

Tipiracil hydrochloride

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride or 2,4(1*H*,3*H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1) and has the following structural formula:



Tipiracil hydrochloride has a molecular formula $C_9H_{11}ClN_4O_2$•HCl and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

LONSURF (trifluridine and tipiracil) tablets for oral use contain 15 mg of trifluridine and 6.14 mg of tipiracil equivalent to 7.065 mg of tipiracil hydrochloride or 20 mg of trifluridine and 8.19 mg of tipiracil equivalent to 9.420 mg of tipiracil hydrochloride.

LONSURF tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate. The tablets are imprinted with ink containing shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LONSURF consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against *KRAS* wild-type and mutant human colorectal cancer xenografts in mice.

12.2 Pharmacodynamics

Cardiac Electrophysiology

LONSURF administered to 42 patients with advanced solid tumors at the recommended dosage had no large effect (i.e. >20 ms) in the mean QTc interval when compared to placebo and no exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc >500 msec and 2.4% had a QTc increase from baseline >60 msec.

12.3 Pharmacokinetics

After twice daily dosing of LONSURF, systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 mg/m^2 (0.43 times the recommended dose) to 35 mg/m^2.

The accumulation of trifluridine was 3-fold for $AUC_{0\text{-}12hr}$ and 2-fold for C_{max} at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of LONSURF 35 mg/m^2 increased the mean $AUC_{0\text{-}last}$ of trifluridine by 37-fold and C_{max} by 22-fold with reduced variability compared to administration of a single dose of trifluridine 35 mg/m^2 alone.

Absorption

Following a single oral administration of LONSURF at 35 mg/m^2 in patients with cancer, the mean time to peak plasma concentration (T_{max}) of trifluridine was around 2 hours.

Food Effect

A standardized high-fat, high-calorie meal decreased trifluridine C_{max}, tipiracil C_{max} and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in patients with cancer following administration of a single dose of LONSURF 35 mg/m^2.

Distribution

Trifluridine mainly binds to human serum albumin. The in vitro protein binding of trifluridine in human plasma is >96%, independent of drug concentration and presence of tipiracil. Plasma protein binding of tipiracil is below 8%.

Elimination

After administration of LONSURF 35 mg/m^2, the mean elimination half-life ($t_{1/2}$) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours.

Metabolism

Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). No other major metabolites were detected in plasma or urine.

Excretion

After single oral administration of LONSURF (60 mg) with [^{14}C]-trifluridine, the total cumulative excretion of radioactivity was 60% of the administered dose. The majority of recovered radioactivity was eliminated into urine (55% of the dose) as FTY and trifluridine glucuronide isomers within 24 hours and the excretion into feces and expired air was <3% for both. The unchanged trifluridine was <3% of administered dose recovered in the urine and feces.

After single oral administration of LONSURF (60 mg) with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion. Tipiracil was the major component and 6-HMU was the major metabolite in urine, and feces.

Specific Populations

Based on the population pharmacokinetic analysis, there is no clinically relevant effect of age, sex, or race (White or Asian) on the pharmacokinetics of trifluridine or tipiracil.

Patients with Renal Impairment

In a dedicated renal impairment study, all patients received LONSURF 35 mg/m^2 twice daily except for patients with severe renal impairment who received 20 mg/m^2 twice daily. Mild renal impairment (CLcr of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect on steady-state $AUC_{0\text{-last}}$ of trifluridine and tipiracil. Moderate renal impairment (CLcr of 30 to 59 mL/min) increased steady-state $AUC_{0\text{-last}}$ of trifluridine by 56% and tipiracil by 139% compared to normal renal function (CLcr ≥ 90 mL/min). Severe renal

impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state $AUC_{0\text{-last}}$ of trifluridine by 140% and tipiracil by 614% compared to normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

Patients with Hepatic Impairment

No clinically important differences in the mean exposures of trifluridine and tipiracil were observed between patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST ≤ ULN); however, 5 of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe hepatic impairment *[see Dosage Modifications (2.2), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

In vitro studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.

In vitro studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Trifluridine/tipiracil was genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammalian-cultured cells, and a micronucleus test in mice.

Animal studies did not indicate an effect of trifluridine/tipiracil on male fertility in rats. Dose-related increases in the corpus luteum count and implanted embryo count were observed, but female fertility was not affected.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer

The efficacy of LONSURF was evaluated in RECOURSE (NCT01607957), an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (mCRC). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG performance status (PS) 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients were randomized 2:1 to receive LONSURF 35 mg/m^2 or matching placebo orally twice daily after meals on Days 1-5 and 8-12 of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months), and region (Japan vs. US,

Europe and Australia). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab.

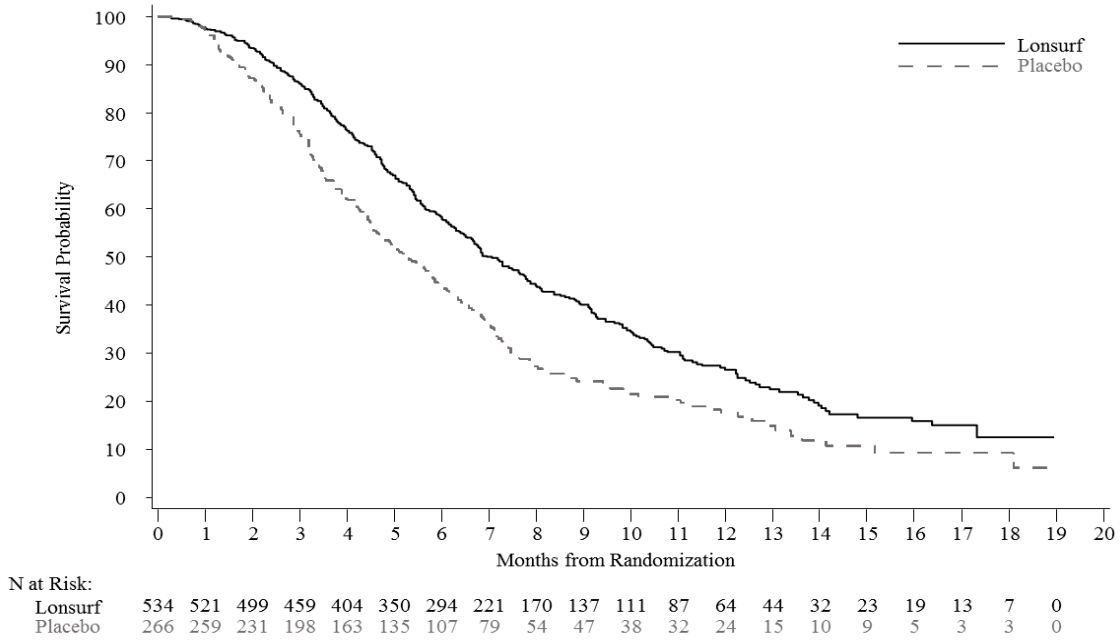
Efficacy results are summarized in Table 7 and Figure 1.

Table 7 Efficacy Results from RECOURSE

	LONSURF (N=534)	**Placebo (N=266)**
Overall Survival		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months)[a] (95% CI)[b]	7.1 (6.5, 7.8)	5.3 (4.6, 6.0)
Hazard ratio (95% CI)	0.68 (0.58, 0.81)	
p-value[c]	<0.001	
Progression-Free Survival		
Number of events, N (%)	472 (88)	251 (94)
Hazard ratio (95% CI)	0.47 (0.40, 0.55)	
p-value[c]	<0.001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region), 2-sided

Figure 1 Kaplan-Meier Curves of Overall Survival in RECOURSE



14.2 Metastatic Gastric Cancer

The efficacy of LONSURF was evaluated in TAGS (NCT02500043), an international, randomized, double-blind, placebo-controlled study in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior regimens for advanced disease. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Other key eligibility criteria included ECOG performance status (PS) 0 or 1. Patients were randomized 2:1 to receive LONSURF 35 mg/m^2 orally twice daily on Days 1-5 and 8-12 of each 28-day cycle with best supportive care (BSC) or matching placebo with BSC until disease progression or unacceptable toxicity. Randomization was stratified by ECOG PS at baseline (0 vs. 1), prior ramucirumab (yes vs. no), and geographic region (Japan vs. rest of world). The major efficacy outcome measure was OS and an additional outcome measure was PFS.

A total of 507 patients were randomized to LONSURF (N=337) or placebo (N=170). The median age was 63 years, 73% were male, 70% and 16% were White and Asian respectively, and 38% had a baseline ECOG PS of 0. Seventy-one percent of patients had gastric tumors, 29% had GEJ tumors, and two patients had gastric/GEJ tumors. All patients received platinum-based chemotherapy, 99% received fluoropyrimidine-based therapy, 91% received a taxane, 55% received irinotecan, and 33% received ramucirumab. The HER2 status was negative in 62%, positive in 19%, and unknown in 20% of patients. Among the 94 patients with HER2 positive tumors, 89% received prior anti-HER2 therapy.

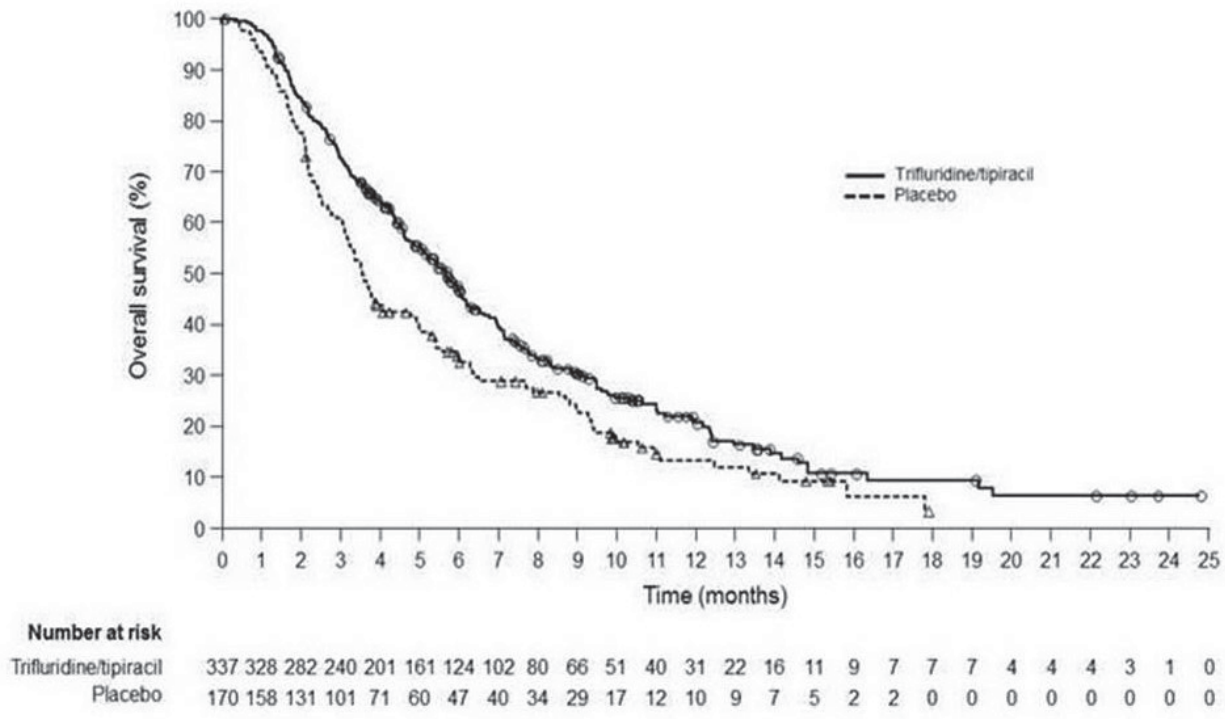
Efficacy results are summarized in Table 8 and Figure 2.

Table 8 Efficacy Results from TAGS

	LONSURF (N=337)	Placebo (N=170)
Overall Survival		
Number of deaths, N (%)	244 (72)	140 (82)
Median OS (months)[a] (95% CI)[b]	5.7 (4.8, 6.2)	3.6 (3.1, 4.1)
Hazard ratio (95% CI)	0.69 (0.56, 0.85)	
p-value[c]	0.0006	
Progression-Free Survival		
Number of events, N (%)	287 (85)	156 (92)
Hazard ratio (95% CI)	0.56 (0.46, 0.68)	
p-value[c]	<0.0001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: ECOG PS, prior ramucirumab treatment, region), 2-sided

Figure 2 Kaplan-Meier Curves of Overall Survival in TAGS



15 REFERENCES

1. "OSHA Hazardous Drugs". OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

LONSURF 15 mg/6.14 mg tablets are supplied as white, biconvex, round, film-coated tablet, imprinted with '15' on one side, and '102' and '15 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1025-1
- 40 count: NDC 64842-1025-2
- 60 count: NDC 64842-1025-3

LONSURF 20 mg/8.19 mg tablets are supplied as pale red, biconvex, round, film-coated tablet, imprinted with '20' on one side, and '102' and '20 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1020-1
- 40 count: NDC 64842-1020-2
- 60 count: NDC 64842-1020-3

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

If stored outside of original bottle, discard after 30 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Myelosuppression

Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Toxicity

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain *[see Adverse Reactions (6.1)]*.

Administration Instructions

Advise patients that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dosage.

Advise patients to take LONSURF with food *[see Dosage and Administration (2.1)]*.

Advise patients that anyone else who handles their medication should wear gloves *[*see *References (15)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2), Use in Specific Populations (8.3)]*.

Advise female patients of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose *[see Warnings and Precautions (5.2), Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by: Taiho Pharmaceutical Co., Ltd., Japan
Manufactured for: Taiho Oncology, Inc., Princeton, NJ 08540 USA

LONSURF is a registered trademark of Taiho Pharmaceutical Co., Ltd used under license by Taiho Oncology, Inc.

PATIENT INFORMATION
LONSURF® (LON-serf)
(trifluridine and tipiracil)
tablets

What is the most important information I should know about LONSURF?

Your healthcare provider should do blood tests before you receive LONSURF, at day 15 during treatment with LONSURF, and as needed to check your blood cell counts.

LONSURF may cause serious side effects, including:

Low blood cell counts. Low blood counts are common with LONSURF and can sometimes be severe and life-threatening. LONSURF can cause a decrease in your white blood cells, red blood cells, and platelets. Low white blood cells can make you more likely to get serious infections that could lead to death. Your healthcare provider may:

- lower your dose of LONSURF or stop LONSURF if you have low white blood cell or low platelet counts.

Tell your healthcare provider right away if you get any of the following signs and symptoms of infection during treatment with LONSURF:

- fever
- chills
- body aches

See **"What are the possible side effects of LONSURF?"** for more information about side effects.

What is LONSURF?

LONSURF is a prescription medicine used to treat people with

- colorectal cancer that has spread to other parts of the body and who have been previously treated or cannot receive certain chemotherapy medicines.
- a kind of stomach cancer called gastric cancer including adenocarcinoma of the gastroesophageal junction that has spread to other parts of the body and who have been previously treated or cannot receive certain chemotherapy medications.

It is not known if LONSURF is safe and effective in children.

Before you take LONSURF, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney or liver problems
- are pregnant or plan to become pregnant. LONSURF can harm your unborn baby.
  For females who can become pregnant:
  - Your healthcare provider will verify your pregnancy status before you start treatment with LONSURF.
  - You should use effective birth control during treatment with LONSURF and for at least 6 months after your last dose of LONSURF.
  - Tell your healthcare provider right away if you become pregnant.

  For males:
  - You should use a condom during sex with female partners who are able to become pregnant during your treatment with LONSURF and for 3 months after your last dose of LONSURF. Tell your healthcare provider right away if your partner becomes pregnant while you are taking LONSURF.
- are breastfeeding or plan to breastfeed. It is not known if LONSURF passes into breast milk. Do not breastfeed during treatment with LONSURF and for one day after your last dose of LONSURF.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take LONSURF?

- Take LONSURF exactly as your healthcare provider tells you.
  LONSURF comes in two strengths. Your healthcare provider may prescribe both strengths for your prescribed dose.
- Take LONSURF 2 times a day with food.
- Swallow LONSURF tablets whole.
- Your caregiver should wear gloves when handling LONSURF tablets.
- If you miss a dose of LONSURF, do not take additional doses to make up for the missed dose. Call your healthcare provider for instructions about what to do for a missed dose.
- Wash your hands after handling the LONSURF tablets.

What are the possible side effects of LONSURF?

LONSURF may cause serious side effects, including:

- See **"What is the most important information I should know about LONSURF?"**

The most common side effects of LONSURF include:

- Tiredness (fatigue, weakness)
- nausea
- decreased appetite
- diarrhea
- vomiting
- abdominal pain
- fever

Tell your healthcare provider if you have nausea, vomiting, or diarrhea that is severe or that does not go away.

These are not all of the possible side effects of LONSURF. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LONSURF?

- Store LONSURF at room temperature between 68°F and 77°F (20°C and 25°C).
- If you store LONSURF outside of the original bottle, throw away (dispose of) any unused LONSURF tablets after 30 days.
- Talk to your healthcare provider about how to safely dispose of LONSURF.

Keep LONSURF and all medicines out of the reach of children.

General information about the safe and effective use of LONSURF

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LONSURF for a condition for which it was not prescribed. Do not give LONSURF to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about LONSURF that is written for health professionals.

What are the ingredients in LONSURF?

Active ingredients: trifluridine and tipiracil hydrochloride

Other ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide (20 mg tablet only), and magnesium stearate

Imprinting ink: shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

Manufactured by: Taiho Pharmaceutical Co., Ltd., Japan
Manufactured for: Taiho Oncology, Inc., Princeton, NJ 08540 USA
 For more information, go to www.Lonsurf.com or call 1-844-878-2446.

This Patient Informa ion has been approved by the U.S. Food and Drug Administration Revised: 2/2019

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
NDA	207981/Labeling Supplement 9
Type/Category	PMR/PMC Final Report (SDN 312)
Brand Name	LONSURF®
Generic name	TAS-102: Trifluridine (FTD)/Tipiracil (TPI)
Approved Indications	Metastatic colorectal cancer Metastatic gastric or gastroesophageal junction adenocarcinoma
Dosage Form and Strengths	Tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil
Route of Administration	Oral
Dosing Regimen	35 mg/m^2 dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle
Sponsor	Taiho Oncology, Inc.
OCP Division	DCPV
OND Division	DOP2
Submission Date	6/24/2019
PDUFA	12/24/2019
Primary Reviewer	Yibo Wang, Ph.D.
Team Lead	Hong Zhao, Ph.D.

1 EXECUTIVE SUMMARY

Lonsurf® (trifluridine and tipiracil, TAS-102) is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor. Lonsurf was approved on September 22, 2015 for the treatment of adult patients with:

- metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.
- metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

The approval letter included a post market requirement (PMR) for a dedicated renal impairment (RI) study (PMR 2963-2).

Study TAS-102-107 evaluated the safety, tolerability, and pharmacokinetics (PK) of TAS-102 in advanced solid tumor patients with varying degrees of RI. A reduced dose of 20 mg/m^2 BID was selected for patients with severe RI in the study.

The trial results showed that severe RI increased the steady-state AUC (dose-normalized) of trifluridine by 2.4-fold. Patients with severe RI who received a reduced dose of 20 mg/m^2/dose did not show a meaningful change in safety findings compared to patients with normal renal function and mild RI who received a dose of 35 mg/m^2/dose. Therefore, a dose of TAS-102 at 20 mg/m^2 twice daily (BID) is appropriate and tolerable for patients with severe RI.

The trial results indicated that mild to moderate RI had no clinically meaningful effects on the exposures of trifluridine. In addition, the safety findings in patients with mild and moderate RI were consistent with the currently known safety profile in this population. Therefore, no dose adjustment is needed for patients with mild and moderate RI.

Taiho proposed modifications to the following labeling sections: Use in Specific Populations (section 8) and Clinical Pharmacology (section 12.3) to incorporate the information obtained in the RI study.

2 RECOMMENDATIONS

This labeling supplement is acceptable from a clinical pharmacology perspective as Taiho and the FDA have come to an agreement regarding the labeling modifications. PMR 2963-2 is considered fulfilled.

3 BACKGROUND

Lonsurf consists of a thymidine-based nucleoside analog, trifluridine (FTD), and the thymidine phosphorylase inhibitor, tipiracil (TPI), at a molar ratio 1:0.5 (weight ratio, 1:0.471). Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against KRAS wild-type and mutant human colorectal cancer xenografts in mice.

After administration of Lonsurf 35 mg/m^2, the mean elimination half-life ($t_{1/2}$) after a single dose was 1.4 hours for trifluridine and 2.1 hours for tipiracil. The mean $t_{1/2}$at steady-state was 2.1 hours for trifluridine and 2.4 hours for tipiracil. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes and no other major metabolites were detected in plasma or urine.

After single oral administration of Lonsurf (60 mg) with [^{14}C]-trifluridine, the total cumulative excretion of radioactivity was 60% of the administered dose. The majority of recovered radioactivity was eliminated into urine (55% of the dose) as FTY and trifluridine glucuronide isomers within 24 hours and the excretion into feces and expired air was <3% for both. The unchanged trifluridine was <3% of administered dose recovered in the urine and feces.

After single oral administration of Lonsurf (60 mg) with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion. Tipiracil was the major component and 6-HMU was the major metabolite in urine, and feces.

In the Phase 3, multinational, randomized, double-blind study (RECOURSE) with 533 patients treated with TAS-102, using the Cockcroft-Gault formula for calculation of creatinine clearance (CLcr), the estimated mean AUC of trifluridine at steady state was 31% higher in patients with mild RI (CLcr = 60 to 89 mL/min) and 43% higher in patients with moderate RI (CLcr = 30 to 59 mL/min) than that in patients with normal renal function (CLcr ≥ 90 mL/min). The estimated mean AUC of tipiracil was 34% higher in patients with mild RI and 65% higher in patients with moderate RI than that in patients with normal renal function. No adjustment to the starting dosage of Lonsurf is recommended in patients with mild or moderate RI (CLcr of 30 to 89 mL/min). The PK of trifluridine and tipiracil have not been studied in patients with severe RI (CLcr < 30 mL/min) or end-stage renal disease. Therefore, Taiho was required to complete a PK trial as a PMR to determine the appropriate dose of Lonsurf in patients with severe RI.

4 RI STUDY (PMR 2963-2)

4.1 STUDY DESIGN

Study TAS-102-107 compared the safety, tolerability, and PK profiles of TAS-102 across the RI groups (Cohorts 1, 2, and 3) and patients with normal renal function (Cohort 0) to detect clinically relevant differences. This study was conducted in 2 parts (PK part and Extension part).

PK part (Cycle 1):

Patients were enrolled into the following 3 cohorts in parallel according to baseline renal function based on estimated CLcr:

- Cohort 0: Normal renal function (CLcr ≥ 90 mL/min);
- Cohort 1: Mild RI (CLcr of 60 to 89 mL/min/);
- Cohort 2: Moderate RI (CLcr of 30 to 59 mL/min/).

Lonsurf was administered orally BID at a dose of 35 mg/m^2 on Days 1 through 5 and Days 8 through 12 of a 28-day cycle within 1 hour after completing morning and evening meals as recommended by the Lonsurf label. An interim assessment was performed to assess the safety, tolerability, and PK of the first 3 cohorts. Based on the clinically relevant differences observed among the control group (Cohort 0) and Cohorts 1 (mild RI) and 2 (moderate RI), 20 mg/m^2/dose BID was selected as the starting dose for Cohort 3 (severe RI, CLcr of 15 to 29 mL/min).

The Cockcroft-Gault (C-G) formula was used to estimate CLcr (mL/min):

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \{\times 0.85 \text{ if female}\}$$

Approximately 12 patients were planned to be enrolled in each of Cohorts 0, 1, and 2 to ensure a sufficient number (approximately 9) of evaluable patients in each cohort. For the cohort with severe RI (Cohort 3), a total of 6 PK-evaluable patients were planned to be enrolled to ensure adequate data for PK analysis. Actual enrollment was 12 patients with normal renal function, and 12, 11, and 8 patients with mild, moderate, and severe RI, respectively. Within each of the first 2 cohorts, patients could be enrolled in parallel. In Cohort 3, the first 3 patients were enrolled sequentially such that the second and third patients were not enrolled until after the previous patient completed Cycle 1 with acceptable safety and tolerability as determined by the Investigator and the Sponsor. After the third patient completed Cycle 1 with acceptable safety and tolerability, the remaining patients could be enrolled at the same time. A starting dose of 20 mg/m^2 BID was established for Cohort 3 per Taiho's rationales provided in Section 7.3 Selection of Dose of the clinical study report.

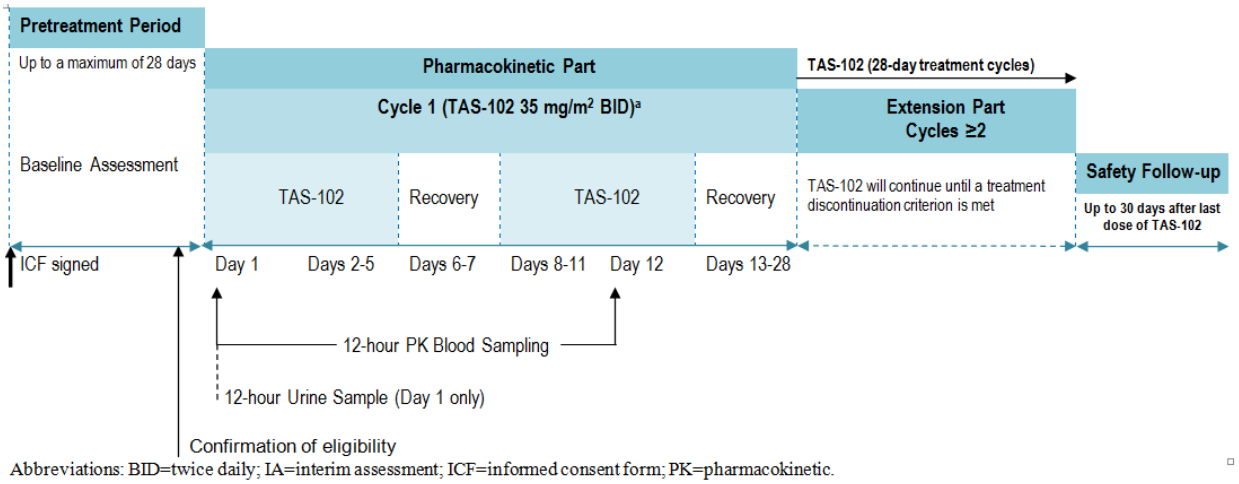
Blood samples were collected on Day 1 and Day 12 at the following time points relative to the first dose (AM dosing): pre-dose (within 30 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post AM dose. The 12-hour post-dose PK sample was taken before administration of the PM dose. Urine samples for PK analysis were collected on Day 1 prior to morning (AM) dosing (pre-dose) and 0 to 12 hours post-AM dose. The concentrations of FTD, FTY (major metabolite), and TPI in plasma and urine were measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. PK parameters were calculated for trifluridine and tipiracil in plasma after administration of TAS-102 on Day 1 and Day 12 of Cycle 1 using non-compartmental analyses.

Extension Part (Cycles ≥2):

Patients who completed the PK Part (Cycle 1) entered the Extension Part in which TAS-102 continued to be administered orally BID for 5 days with 2 days rest for 2 weeks, repeated every 4 weeks until the patient met any of the treatment discontinuation criteria. This part is to assess the safety and tolerability of TAS-102 in advanced solid tumor patients with varying degrees of RI in Cycles 2 and beyond. No blood or urine PK samples were collected in the extension part.

The overall study design is shown in Figure 1 below.

Figure 1: Study Schema



Abbreviations: BID=twice daily; IA=interim assessment; ICF=informed consent form; PK=pharmacokinetic.

[a] The dose level for Cohort 3 (severe RI) was determined to be 20 mg/m^2 BID based on the Interim Assessment results for Cohorts 0, 1, and 2.

4.2 DOSE SELECTION RATIONALES

Taiho's position: In Japanese Phase 2 Study J003-10040030, the Phase 3 Studies RECOURSE and TO-TAS-102-302, TAS-102 dose at 35 mg/m^2/dose BID (70 mg/m^2/day for 5 days, with a 2-day rest, for 2 weeks followed by 2 weeks rest) was generally well tolerated in patients with mild and moderate RI in terms of overall safety. Therefore, in the current study TAS-102-107, patients with normal renal function and those with mild and moderate RI (Cohorts 0, 1, and 2) received the same starting dose of TAS-102 used in the RECOURSE study in Cycle 1.

In the current Study TAS-102-107, all patients in the first 3 cohorts (Cohorts 0, 1, and 2) completed Cycle 1 in November 2015. Taiho conducted interim assessment at the data cutoff date of Dec 21, 2015 to assess the safety, tolerability, and PK of the first treatment cycle for the 3 cohorts. patients with moderate and mild RI (RI) tended to show a higher incidence of ≥ Grade 3 adverse events and serious adverse events, compared to patients with normal renal function. However, TAS-102 was well tolerated among patients with mild or moderate RI.

The PK data showed increased FTD AUC_{0-12} of approximately 15% and 50% in patients with mild (Cohort 1) and moderate (Cohort 2) RI, respectively, compared to patients with normal renal function (Cohort 0). Taiho's population PK (PopPK) analysis (Study 12DA25) demonstrated that the mean relative ratio ranges of AUC in patients with mild and moderate RI compared to patients with representative renal function (median CLcr = 103 mL/min) in the study population were 1.08 to 1.32 and 1.33 to 1.87, respectively. The FTD exposure increased with decreasing renal function, indicating that FTD CL/F is correlated with renal function. Based on the Pop PK model analysis, FTD CL/F = $0.3432 \times CLcr^{0.4870}$. FTD CL/F was extrapolated to patients with severe RI to be as approximately half that in patients with normal renal function. Doses of 25 mg/m^2, 20 mg/m^2, and 15 mg/m^2 of TAS-102 in patients with severe RI are expected to have comparable exposure to patients with moderate impairment, mild impairment, and normal renal function, respectively. In addition, the PK of TAS-102 was investigated in a phase 1 study (J001-10040010) with dose levels of 15 mg/m^2 BID up to 35 mg/m^2 BID. The AUC of FTD tended to increase more than expected based on the increase in dose; however, CL/F and apparent volume of distribution (Vd/F) of FTD generally remained constant at the dose range of 20 to 35 mg/m^2. Therefore, dose level of 15 mg/m^2 may cause underexposure of FTD, then affect efficacy. Taiho selected dose level of 20 mg/m^2 as the starting dose for patients with severe RI, which is expected to provide adequate exposure of FTD.

Reviewer's comment: Taiho's dose selection rationale is acceptable.

4.3 BIOANALYTICAL METHOD AND RESULTS

The bioanalytical (LC-MS/MS) methods used to measure the concentrations of FTD, FTY (major metabolite), and TPI in plasma and urine are the same as the ones used in the original NDA submission. The LC-MS/MS methods were reviewed in the original clinical pharmacology review and found acceptable [DARRTS, NDA 207981, REV-CLINPHARM-21 (Primary Review), dated 08/21/2015, page 41-45 of 64]. After the initial submission, Taiho conducted partial validation study to demonstrate validity in the replacement of an autosampler of high-performance liquid chromatograph (HPLC) system. Per the results of the partial validation study No. P14-10427 (August 2015), the modified methods for the determinations of FTD, FTY, and TPI using the replaced autosampler were successfully validated. The table summarized the validation parameters of the method and method performance in the current RI study TAS-102-107 is provided in the appendix of this review.

This method only measured the total concentrations (binding to plasma protein + unbound) of FTD and TPI. Plasma protein binding of TPI is below 8%. Hence, alterations in binding of TPI due to impaired renal function are relatively small. The in vitro protein binding of FTD in human plasma is > 96%, independent of drug concentration and presence of FTD. Therefore, the bioanalytical method used to quantify the plasma total concentrations of the FTD and TPI is acceptable and the bioanalytical results are reliable.

4.4 PK RESULTS

PK-evaluable Population

The PK Population included 41 patients: 40 with evaluable PK concentration data at Cycle 1 Day1, 38 with evaluable PK data at Cycle 1 Day 12, and 37 with evaluable PK data at both time points. A list of patients excluded from the PK analysis is provided in Table 1 below.

Table 1. Patients Excluded from the PK Analysis

Patient Number	Renal Function Cohort	Visit	Reason for Exclusion from PK Evaluability
(b) (6)	Normal	Cycle 1 Day 1	AM dose was taken prior to the AM meal.
	Normal	Cycle 1 Day 12	AM dose was taken more than 1 hour after completion of the AM meal.
	Normal	Cycle 1 Day 1 Cycle 1 Day 12	AM dose was taken more than 1 hour after completion of the AM meal.
	Moderate renal Impairment	Cycle 1 Day 12	Not done.
	Severe renal Impairment	Cycle 1 Day 12	Not done.
	Severe renal Impairment	Cycle 1 Day 1 Cycle 1 Day 12	The wrong dose was taken.

AM = ante meridiem; PK = pharmacokinetics
Source: Listing 16.2.5.2.1

Source: Table 10, Clinical Study Report No. TAS-102-107 (page 59)

Reviewer's comment: Patients # (b) (6), (b) (6), (b) (6) were exclude from the PK analysis because they either took the drug before meal or 1 hour after meal. Per the Lonsurf label, compared to the fasted conditions, a standard high-fat, high-calorie meal decreased trifluridine Cmax and tipiracil Cmax and AUC by approximately 40%, with no change in trifluridine AUC following administration of a single dose of Lonsurf 35 mg/m^2. Patients should be advised to take Lonsurf with food. It is recommended to take Lonsurf within 1 hour after completion of the morning and evening meals based on the observed correlation between the increase in the Cmax of FTD and the decrease in neutrophil counts [DARRTS, NDA 207981, REV-CLINPHARM-21 (Primary Review), dated 08/21/2015]. Therefore, these 3 patients were excluded from PK analysis because they did not take Lonsurf within 1 hour after completion of the morning meal and the PK parameter were affected. For patients # (b) (6) and # (b) (6), PK samples were not collected on C1D12. For patient # (b) (6) in the severe RI cohort, the body surface area was 1.92 m^2. This patient should have been given a dose of 35 mg BID (70 mg daily) per Table 5 in the study protocol; however, patient # (b) (6) was dosed 80 mg daily on Cycle 1 and Cycle 2. Hence, the PK data from this patient was excluded because incorrect dose was given. The reviewer agrees that the above-mentioned patients in specific visit should be excluded from the PK analysis.

The same dose (35 mg/m^2 BID) was used for the normal renal function, mild, and moderate RI cohorts. For the severe RI cohort, dose was adjusted to 20 mg/m^2 BID. The PK parameters calculated by Taiho were not dose-normalized. The reviewer conducted the analysis using dose-normalized PK parameters by converting the PK parameters for the severe RI cohort by a factor of 35/20 since the $AUC_{0\text{-}10h}$ for trifluridine at the dose range of 20 to 35 mg/m^2 BID was approximately dose proportional.

PK Data Analyses

Plasma PK Results for FTD

In Study TAS-102-107, the dose-normalized Cmax and AUC of FTD on Cycle 1 Day1 (C1D1) were comparable among the normal renal function, mild, moderate, and severe RI cohorts. The dose-normalized mean $AUC_{0\text{-}last}$ and AUC_{tau} values of FTD on C1D12 increased as the degree of RI increased (severe>moderate>mild>normal). On C1D12, the dose-normalized mean Cmax values was the highest (7284 ng/mL) in the severe RI cohort, compared to that of moderate RI (6014 ng/mL), mild RI (4763 ng/mL), and normal (5235 ng/mL) cohorts. The repeat dosing increased Cmax by 2-fold (R_{Cmax}) irrespective of the degree of RI. The accumulation ratio of $AUC_{0\text{-}last}$ ($R_{AUC0\text{-}last}$) increased (2.8-6.1 fold) as RI increased (Table 2).

Table 2. PK Parameters of Trifluridine (FTD) Cycle 1 Day 1 and Day 12

Cohort Visit	Statistic	T_{max} [hr]	$T_{1/2}$ [hr]	C_{max} [ng/mL]	$AUC_{0\text{-}last}$ [hr*ng/mL]	$AUC_{0\text{-}inf}$ (day 1) or AUC_{tau} (day 12) [hr*ng/mL]	CL/F (day 1) or CLss/F (day 12) [L/hr]	Vd/F (day 1) [L]	R_{Cmax} (day 12)	$R_{AUC0\text{-}last}$ (day 12)
Cycle 1 Day 1										
Normal Cohort (N = 11)	n	10	10	10	10	10	10	10	NA	NA
	Mean	1.86	1.21	2882	7824	7870	8.72	15.47	NA	NA
	SD	1.54	0.38	1372	2830	2818	4.19	12.22	NA	NA
	CV (%)	82.7	31.8	47.6	36.2	35.8	48.1	79.0	NA	NA
Mild Renal Impairment Cohort (N=12)	n	12	12	12	12	12	12	12	NA	NA
	Mean	1.26	2.22	3161	7192	7328	10.05	29.89	NA	NA
	SD	0.92	1.15	1363	2539	2668	5.96	16.91	NA	NA
	CV (%)	73.1	51.7	43.1	35.3	36.4	59.3	56.6	NA	NA
Moderate Renal Impairment Cohort (N=11)	n	11	11	11	11	11	11	11	NA	NA
	Mean	1.78	1.92	2763	7939	8138	9.17	24.70	NA	NA
	SD	1.52	0.43	1362	3457	3556	4.86	11.39	NA	NA
	CV (%)	85.2	22.3	49.3	43.5	43.7	53.0	46.1	NA	NA
Severe Renal Impairment Cohort (N=7)	n	7	7	7	7	7	7	7	NA	NA
	Mean	1.18	2.78	1778	4043	4239	12.69	34.70	NA	NA
	SD	1.14	1.43	929	1706	1822	12.41	10.50	NA	NA
	CV (%)	96.0	51.4	52.2	42.2	43.0	97.8	30.2	NA	NA

Cohort Visit	Statistic	T_{max} [hr]	$T_{1/2}$ [hr]	C_{max} [ng/mL]	$AUC_{0\text{-last}}$ [hr*ng/mL]	$AUC_{0\text{-inf}}$ (day 1) or AUC_{tau} (day 12) [hr*ng/mL]	CL/F (day 1) or CLss/F (day 12) [L/hr]	Vd/F (day 1) [L]	R_{Cmax} (day 12)	$R_{AUC0\text{-last}}$ (day 12)
Cycle 1 Day 12										
Normal Cohort (N=11)	n	10	10	10	10	10	10	NA	9	9
	Mean	1.36	2.23	5235	19743	20131	3.29	NA	2.25	2.80
	SD	0.71	0.98	2662	6895	7398	1.12	NA	1.53	1.18
	CV (%)	52.3	44.0	50.9	34.9	36.8	34.0	NA	68.3	42.1
Mild Renal Impairment Cohort (N=12)	n	12	12	12	12	12	12	NA	12	12
	Mean	2.35	2.25	4763	22201	22539	4.07	NA	1.66	3.05
	SD	1.30	0.76	2573	13026	13320	3.54	NA	1.09	1.55
	CV (%)	55.6	33.7	54.0	58.7	59.1	87.1	NA	65.3	50.9
Moderate Renal Impairment Cohort (N=11)	n	10	8	10	10	8	8	NA	10	10
	Mean	2.56	2.98	6014	31374	30398	2.10	NA	2.42	4.31
	SD	1.81	0.91	2273	12894	7742	0.41	NA	1.28	1.52
	CV (%)	70.8	30.4	37.8	41.1	25.5	19.6	NA	52.8	35.4
Severe Renal Impairment Cohort (N=7)	n	6	1	6	6	3	1	NA	6	6
	Mean	1.88	3.30	4162	27495	30614	1.90	NA	2.41	6.09
	SD	1.12	NA	1728	12682	18278	NA	NA	0.97	2.25
	CV (%)	59.8	NA	41.5	46.1	59.7	NA	NA	40.1	36.9

Source: Table 11, Clinical Study Report No. TAS-102-107 (page 64-65)

Plasma PK Results for TPI

The mean $AUC_{0\text{-last}}$ value of TPI significantly increased with increasing degree of RI with the highest values obtained in patients with severe RI despite adjustment of the dose. In the severe RI group, although $AUC_{0\text{-inf}}$ and AUC_{tau} values were not calculable for all the patients (n=1 for C1D1; n=2 for C1D12), the trend was consistent with $AUC_{0\text{-last}}$. An increase in degree of RI decreased mean CL/F and CLss/F values; however, the mean accumulation ratios of Cmax (R_{Cmax}) and $AUC_{0\text{-last}}$ ($R_{AUC0\text{-last}}$) were comparable among cohorts (Table 3).

Table 3. PK Parameters of Tipiracil (TPI) C1D1 and C1D12

Cohort Visit	Statistic	T_{max} [hr]	$T_{1/2}$ [hr]	C_{max} [ng/mL]	$AUC_{0\text{-last}}$ [hr*ng/mL]	$AUC_{0\text{-inf}}$ (day 1) or AUC_{tau} (day 12) [hr*ng/mL]	CL/F (day 1) or CLss/F (day 12) [L/hr]	Vd/F (day 1) [L]	R_{Cmax} (day 12)	$R_{AUC0\text{-last}}$ (day 12)
Cycle 1 Day 1										
Normal Cohort (N=11)	n	10	9	10	10	9	9	9	NA	NA
	Mean	3.00	2.20	46.52	223.53	233.97	147.90	487.59	NA	NA
	SD	1.06	0.50	18.33	99.23	120.81	80.75	330.55	NA	NA
	CV (%)	35.4	22.7	39.4	44.4	51.6	54.6	67.8	NA	NA
Mild Renal Impairment Cohort (N=12)	n	12	11	12	12	11	11	11	NA	NA
	Mean	2.71	2.44	93.93	402.49	381.44	104.95	414.67	NA	NA
	SD	1.11	0.76	40.86	219.47	196.36	86.18	501.75	NA	NA
	CV (%)	41.2	31.3	43.5	54.5	51.5	82.1	121.0	NA	NA
Moderate Renal Impairment Cohort (N=11)	n	11	10	11	11	10	10	10	NA	NA
	Mean	3.36	2.59	100.38	486.62	495.78	64.62	239.41	NA	NA
	SD	1.52	0.42	40.20	189.38	183.08	18.57	71.74	NA	NA
	CV (%)	45.2	16.3	40.0	38.9	36.9	28.7	30.0	NA	NA
Severe Renal Impairment Cohort (N=7)	n	7	1	7	7	1	1	1	NA	NA
	Mean	3.69	4.00	94.39	681.85	819.59	20.11	116.05	NA	NA
	SD	1.40	NA	24.63	156.86	NA	NA	NA	NA	NA
	CV (%)	38.1	NA	26.1	23.0	NA	NA	NA	NA	NA

Cohort Visit	Statistic	T_{max} [hr]	$T_{1/2}$ [hr]	C_{max} [ng/mL]	$AUC_{0\text{-last}}$ [hr*ng/mL]	$AUC_{0\text{-inf}}$ (day 1) or AUC_{tau} (day 12) [hr*ng/mL]	CL/F (day 1) or CL_{SS}/F (day 12) [L/hr]	Vd/F (day 1) [L]	R_{Cmax} (day 12)	$R_{AUC0\text{-last}}$ (day 12)
Cycle 1 Day 12										
Normal Cohort (N=11)	n	10	9	10	10	9	9	NA	9	9
	Mean	3.19	2.77	48.78	247.70	247.27	128.32	NA	1.19	1.31
	SD	1.89	0.88	21.88	91.01	99.68	58.13	NA	0.54	0.58
	CV (%)	59.5	31.7	44.9	36.7	40.3	45.3	NA	45.2	44.3
Mild Renal Impairment Cohort (N=12)	n	12	10	12	12	10	10	NA	12	12
	Mean	2.91	2.49	77.62	359.39	401.89	78.88	NA	0.91	1.06
	SD	1.13	0.74	43.25	138.54	116.10	21.15	NA	0.50	0.41
	CV (%)	38.9	29.6	55.7	38.5	28.9	26.8	NA	54.9	38.6
Moderate Renal Impairment Cohort (N=11)	n	10	8	10	10	8	8	NA	10	10
	Mean	3.45	2.95	111.67	633.11	602.09	61.97	NA	1.21	1.38
	SD	1.96	0.50	53.49	295.82	321.17	32.74	NA	0.48	0.62
	CV (%)	56.8	16.9	47.9	46.7	53.3	52.8	NA	39.8	45.3
Severe Renal Impairment Cohort (N=7)	n	6	0	6	6	2	0	NA	6	6
	Mean	4.25	--	126.33	1086.02	1719.84	--	NA	1.38	1.57
	SD	2.31	--	54.02	611.76	657.84	--	NA	0.57	0.61
	CV (%)	54.5	--	42.8	56.3	38.3	--	NA	41.2	38.7

Source: Table 18, Clinical Study Report No. TAS-102-107 (page 75)

Urine PK Results

All the urine PK parameters were highly variable with the Coefficient of variation (CV) ranging from 83% to 208%. For FTD, mean values tended to be low for severe RI cohort with no marked differences among all cohorts (Table 4). For TPI, the mean CLr value significantly decreased as the degrees of RI increased. The mean CLr value in the severe RI cohort was approximately 3-fold less than that in normal renal function cohort (Table 5).

Table 4. Pharmacokinetics Parameters of FTD in Urine (PK Population)

Cohort Visit	Nominal time	Statistic	Ae (mg)	Fe (%)	CLr (L/hr)
Normal Cohort	0-12 hr	n	9	9	9
		Mean	0.72	1.22	0.09
		SD	0.77	1.21	0.08
		CV (%)	106.8	99.0	83.3
Mild Renal Impairment Cohort	0-12 hr	n	12	12	12
		Mean	1.50	2.64	0.21
		SD	2.06	3.96	0.34
		CV (%)	137.3	150.0	161.5
Moderate Renal Impairment Cohort	0-12 hr	n	9	9	9
		Mean	1.63	2.63	0.14
		SD	3.29	5.47	0.21
		CV (%)	201.7	208.0	155.4
Severe Renal Impairment Cohort	0-12 hr	n	6	6	6
		Mean	0.14	0.36	0.03
		SD	0.21	0.57	0.04
		CV (%)	155.2	156.4	157.2

Ae = Total urinary excretion; CLr = clearance; CV = coefficient of variation for mean; Fe% = Total urinary excretion normalized by molecular weight as % of dose; FTD = trifluridine; n=Number of patients with data available; PK = pharmacokinetics; SD = standard deviation

Source: Table 14, Clinical Study Report No. TAS-102-107 (page 71)

Table 5. Pharmacokinetics Parameters of TPI in Urine (PK Population)

Cohort Visit	Nominal Time	Statistic	Ae (mg)	Fe%	CLr (L/hr)
Normal Cohort	0-12 hr	n	9	9	9
		Mean	3.76	14.17	16.53
		SD	1.78	7.19	8.12
		CV (%)	47.3	50.8	49.2
Mild Renal Impairment Cohort	0-12 hr	n	12	12	12
		Mean	3.86	13.54	10.34
		SD	2.55	9.40	4.80
		CV (%)	65.9	69.4	46.4
Moderate Renal Impairment Cohort	0-12 hr	n	9	9	9
		Mean	3.76	12.46	7.95
		SD	2.40	7.05	3.82
		CV (%)	63.9	56.6	48.1
Severe Renal Impairment Cohort	0-12 hr	n	6	6	6
		Mean	3.30	19.20	4.84
		SD	1.14	6.84	0.78
		CV (%)	34.5	35.6	16.1

Source: Table 16, Clinical Study Report No. TAS-102-107 (page 73)

Results of Statistical Analysis

Plasma PK Parameters for FTD and TPI were analyzed by a one-way ANOVA using the categorical RI groups as class variables after the PK parameters were log transformed.

On C1D1, Cmax, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ for FTD in the mild and moderate RI cohorts were comparable to those in the normal renal function cohort (Table 6). The Cmax, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ values for FTD in the severe RI cohort after dose normalization were comparable to those in the normal renal function cohort with the geometric mean ratios (GMRs) of 1.08, 0.85, and 0.88, respectively (Table 7). There was no significant difference in CL/F ratio between RI cohorts and the normal renal function. On C1D12, no significant differences were observed for all the PK parameters in mild and moderate RI cohorts compared to the normal renal function cohort (p-value > 0.05). However, the GMRs of moderate RI cohort to normal renal function cohort for $AUC_{0\text{-last}}$ and AUC_{tau} were 1.56 (90% CI [1.08, 2.27]) and 1.56 (90% CI [1.04, 2.33]), respectively. After dose normalization, the GMRs of severe RI cohort to normal renal function cohort for Cmax, $AUC_{0\text{-last}}$ and AUC_{tau} were 1.47, 2.40, and 2.41, respectively (Table 7). CLss/F had a deceasing trend as increasing degree of RI.

Table 6. One-way ANOVA Analysis for Trifluridine (FTD) PK Parameters

PK Parameters	Visit Statistics	Normal Cohort (N=11)	Mild Renal Impairment Cohort (N=12)	Moderate Renal Impairment Cohort (N=11)	Severe Renal Impairment Cohort (N=7)
C_{max} (ng/mL)					
Cycle 1 Day 1	n	10	12	11	7
	Geometric Mean	2514	2896	2494	1557
	Geometric mean ratio to normal cohort		1.15	0.99	0.62
	90% CI for GMR[a]		(0.79, 1.68)	(0.68, 1.45)	(0.40, 0.95)
	P-value for GMR[b]		0.5285	0.9721	0.0689
Cycle 1 Day 12	n	10	12	10	6
	Geometric Mean	4684	4041	5563	3930
	Geometric mean ratio to Normal cohort		0.86	1.19	0.84
	90% CI for GMR[a]		(0.59, 1.26)	(0.80, 1.76)	(0.53, 1.32)
	P-value for GMR[b]		0.5136	0.4670	0.5198
$AUC_{0\text{-}last}$ (hr*ng/mL)					
Cycle 1 Day 1	n	10	12	11	7
	Geometric Mean	7253	6671	7296	3528
	Geometric mean ratio to normal cohort		0.92	1.01	0.49
	90% CI for GMR[a]		(0.65, 1.31)	(0.70, 1.44)	(0.33, 0.73)
	P-value for GMR[b]		0.6887	0.9779	0.0046
Cycle 1 Day 12	n	10	12	10	6
	Geometric Mean	18715	18505	29270	25619
	Geometric mean ratio to Normal cohort		0.99	1.56	1.37
	90% CI for GMR[a]		(0.69, 1.41)	(1.08, 2.27)	(0.89, 2.11)
	P-value for GMR[b]		0.9578	0.0505	0.2261

PK Parameters	Visit Statistics	Normal Cohort (Reference) (N=11)	Mild Renal Impairment Cohort (N=12)	Moderate Renal Impairment Cohort (N=11)	Severe Renal Impairment Cohort (N=7)
$AUC_{0\text{-}inf}$ (Day 1) (hr*ng/mL)					
Cycle 1 Day 1	n	10	12	11	7
	Geometric Mean	7311	6772	7464	3674
	Geometric mean ratio to Normal cohort		0.93	1.02	0.50
	90% CI for GMR[a]		(0.65, 1.32)	(0.71, 1.47)	(0.33, 0.76)
	P-value for GMR[b]		0.7178	0.9236	0.0073
AUC_{tau} (Day 12) (hr*ng/mL)					
Cycle 1 Day 12	n	10	12	8	3
	Geometric Mean	19004	18740	29581	27495
	Geometric mean ratio to normal cohort		0.99	1.56	1.45
	90% CI for GMR[a]		(0.68, 1.42)	(1.04, 2.33)	(0.82, 2.54)
	P-value for GMR[b]		0.9485	0.0738	0.2738
CL/F (Day 1) (L/hr)					
Cycle 1 Day 1	n	10	12	11	7
	Geometric Mean	7.99	9.05	8.26	9.90
	Geometric mean ratio to normal cohort		1.13	1.03	1.24
	90% CI for GMR[a]		(0.80, 1.61)	(0.72, 1.48)	(0.83, 1.86)
	P-value for GMR[b]		0.5544	0.8739	0.3773
CLss/F (Day 12) (L/hr)					
Cycle 1 Day 12	n	10	12	8	1
	Geometric Mean	3.09	3.27	2.07	1.90
	Geometric mean ratio to Normal cohort		1.06	0.67	0.61
	90% CI for GMR[a]		(0.75, 1.49)	(0.46, 0.98)	(0.26, 1.43)
	P-value for GMR[b]		0.7893	0.0852	0.3364

Source: Table 17, Clinical Study Report No. TAS-102-107 (pages 75-76)

Table 7. One-way ANOVA Analysis for Trifluridine (FTD) PK Parameters Comparing Severe RI Cohort to Normal Renal Function Cohort

Geometric Mean		Normal	Severe RI	GMR	90%CI	
C1D1	N	10	7			
	C_{max} (ng/mL)	2514	2725	1.08	0.82	1.43
	$AUC_{0\text{-}last}$ (hr*ng/mL)	7253	6174	0.85	0.66	1.09
	$AUC_{0\text{-}inf}$ (hr*ng/mL)	7311	6429	0.88	0.68	1.13
C1D12	N	10	6			
	C_{max} (ng/mL)	4684	6877	1.47	1.16	1.85
	$AUC_{0\text{-}last}$ (hr*ng/mL)	18715	44833	2.40	1.82	3.15
	AUC_{tau} (hr*ng/mL)	19004	45886	2.41	1.83	3.19

Source: Reviewer generated

On C1D1, Cmax, and $AUC_{0\text{-}last}$ for TPI in the mild, moderate, and severe RI cohorts (dose-normalized) were significantly higher than those in the normal renal function cohort (Table 8 and 9). The GMRs of mild, moderate, and severe RI cohorts to the normal cohort were as follows: 1.91, 2.13, and 3.65 for Cmax; 1.65, 2.21 and 5.68 for $AUC_{0\text{-}last}$; and 1.56, 2.22 and 7.48 for $AUC_{0\text{-}inf}$, respectively. The Cmax and AUCs increased as RI degree increased. The CL/F values were lower in mild, moderate, and severe RI cohorts than that in the normal cohort with GMRs of 0.66 ($p > 0.05$), 0.48 ($p < 0.05$), and 0.15 ($p < 0.05$), respectively.

On C1D12, the same trend was observed in the relationship between PK parameters and degree of RI (Table 8 and 9).. The GMRs of mild, moderate, and severe RI (dose-normalized) cohorts to the normal cohort were as follows: 1.51, 2.27, and 4.51 for Cmax; 1.42, 2.39, and 7.14 for $AUC_{0\text{-}last}$; and 1.68, 2.25, and 7.21 for AUC_{tau}, respectively. RI significantly increased Cmax and AUCs (p values < 0.05). CLss/F was significantly lower in the mild and moderate RI cohorts than that in normal cohort with GMRs of 0.65 and 0.48, respectively.

Table 8. One-way ANOVA Analysis for Tipiracil (TPI) PK Parameters

PK Parameters	Visit Statistics	Normal Cohort (Reference) (N=11)	Mild Renal Impairment Cohort (N=12)	Moderate Renal Impairment Cohort (N=11)	Severe Renal Impairment Cohort (N=7)
C_{max} (ng/mL)					
Cycle 1 Day 1	n	10	12	11	7
	Geometric Mean	43.67	83.56	93.14	91.16
	Geometric mean ratio to normal cohort		1.91	2.13	2.09
	90% CI for GMR[a]		(1.40, 2.62)	(1.55, 2.94)	(1.45, 3.00)
	P-value for GMR[b]		0.0014	0.0003	0.0016
Cycle 1 Day 12	n	10	12	10	6
	Geometric Mean	44.84	67.92	101.67	115.49
	Geometric mean ratio to normal cohort		1.51	2.27	2.58
	90% CI for GMR[a]		(1.07, 2.15)	(1.57, 3.27)	(1.69, 3.93)
	P-value for GMR[b]		0.0532	0.0006	0.0006
$AUC_{0\text{-}last}$ (hr*ng/mL)					
Cycle 1 Day 1	n	10	12	11	7
	Geometric Mean	204.91	338.97	453.45	664.85
	Geometric mean ratio to normal cohort		1.65	2.21	3.24
	90% CI for GMR[a]		(1.16, 2.36)	(1.54, 3.18)	(2.15, 4.89)
	P-value for GMR[b]		0.0225	0.0007	<0.0001
Cycle 1 Day 12	n	10	12	10	6
	Geometric Mean	232.84	331.28	557.39	950.59
	Geometric mean ratio to normal cohort		1.42	2.39	4.08
	90% CI for GMR[a]		(1.00, 2.03)	(1.65, 3.47)	(2.66, 6.26)
	P-value for GMR[b]		0.1015	0.0003	<0.0001

PK Parameters	Visit Statistics	Normal Cohort (Reference) (N=11)	Mild Renal Impairment Cohort (N=12)	Moderate Renal Impairment Cohort (N=11)	Severe Renal Impairment Cohort (N=7)
$AUC_{0\text{-}inf}$ (Day 1) (hr*ng/mL)					
Cycle 1 Day 1	n	9	11	10	1
	Geometric Mean	210.11	327.82	465.46	819.59
	Geometric mean ratio to normal cohort		1.56	2.22	3.90
	90% CI for GMR[a]		(1.05, 2.32)	(1.48, 3.32)	(1.54, 9.88)
	P-value for GMR[b]		0.0665	0.0024	0.0190
AUC_{tau} (Day 12) (hr*ng/mL)					
Cycle 1 Day 12	n	9	10	8	2
	Geometric Mean	230.74	388.17	519.10	1655.74
	Geometric mean ratio to normal cohort		1.68	2.25	7.18
	90% CI for GMR[a]		(1.20, 2.36)	(1.57, 3.22)	(4.03, 12.78)
	P-value for GMR[b]		0.0148	0.0007	<0.0001
CL/F (Day 1) (L/hr)					
Cycle 1 Day 1	n	9	11	10	1
	Geometric Mean	130.51	86.40	62.09	20.11
	Geometric mean ratio to normal cohort		0.66	0.48	0.15
	90% CI for GMR[a]		(0.45, 0.97)	(0.32, 0.70)	(0.06, 0.37)
	P-value for GMR[b]		0.0748	0.0030	0.0013
CLss/F (Day 12) (L/hr)					
Cycle 1 Day 12	n	9	10	8	0
	Geometric Mean	116.82	75.94	55.52	--
	Geometric mean ratio to normal cohort		0.65	0.48	--
	90% CI for GMR[a]		(0.47, 0.91)	(0.33, 0.69)	--
	P-value for GMR[b]		0.0362	0.0014	--

Source: Table 20, Clinical Study Report No. TAS-102-107 (pages 77-78)

Table 9. One-way ANOVA Analysis for TPI PK Parameters Comparing Severe RI Cohort to Normal Renal Function Cohort

Geometric Mean		Normal	Severe RI	GMR	90%CI	
C1D1	N	10	7			
	C_{max} (ng/mL)	43.67	159.52	3.65	2.57	5.18
	$AUC_{0\text{-}last}$ (hr*ng/mL)	204.91	1163.49	5.68	3.61	8.93
	$AUC_{0\text{-}inf}$ (hr*ng/mL)	220.36	1649.21	7.48	4.44	12.62
C1D12	N	10	6			
	C_{max} (ng/mL)	44.84	202.11	4.51	2.94	6.91
	$AUC_{0\text{-}last}$ (hr*ng/mL)	232.84	1663.54	7.14	4.21	12.12
	AUC_{tau} (hr*ng/mL)	237.77	1713.29	7.21	4.24	12.24

Source: Reviewer generated

Taiho further explored the relationships between oral clearance of trifluridine (FTD) on C1D1 or at steady state on C1D12 and the estimated CLcr. The model used the log transformed PK parameters as the dependent variable and the log of the estimated CLcr as the independent variable. The results for regression parameters are presented in Table 10 below. Significant relationships were observed for AUC_{tau} and CLss/F and the estimated CLcr.

Table 10. FTD PK: Effect of estimated CLcr (Regression Analysis Using Power Model)

			Regression Parameters (Power Model) [2]					
					90% CI		95% CI	
Visit	PK Parameters [1]	n	Regression Parameter	Estimate	Lower	Upper	Lower	Upper	P-value
Cycle 1 Day 1	C_{max} (ng/mL)	40	α	6.625	5.620	7.630	5.418	7.832	<.0001
			β	0.284	0.041	0.527	-0.008	0.576	0.0565
	$AUC_{0\text{-}last}$ (hr*ng/mL)	40	α	7.332	6.360	8.303	6.165	8.498	<.0001
			β	0.344	0.109	0.579	0.062	0.626	0.0182
	$AUC_{0\text{-}inf}$ (hr*ng/mL)	40	α	7.428	6.447	8.410	6.249	8.607	<.0001
			β	0.325	0.088	0.563	0.040	0.611	0.0265
	CL/F (L/hr)	40	α	2.550	1.633	3.467	1.449	3.651	<.0001
			β	-0.095	-0.317	0.127	-0.361	0.172	0.4756
	Vd/F (L)	40	α	4.981	4.028	5.934	3.837	6.125	<.0001
			β	-0.461	-0.691	-0.230	-0.738	-0.184	0.0017
	CLr (mL/min)	36	α	-2.190	-5.270	0.889	-5.904	1.523	0.2358
			β	-0.030	-0.744	0.685	-0.891	0.832	0.9439
Cycle 1 Day 12	C_{max} (ng/mL)	38	α	8.398	7.283	9.513	7.058	9.738	<.0001
			β	0.006	-0.263	0.275	-0.317	0.329	0.9699
	$AUC_{0\text{-}last}$ (hr*ng/mL)	38	α	11.360	10.322	12.397	10.114	12.606	<.0001
			β	-0.330	-0.581	-0.080	-0.631	-0.030	0.0320
	AUC_{tau} (hr*ng/mL)	33	α	11.719	10.440	12.998	10.181	13.258	<.0001
			β	-0.410	-0.711	-0.109	-0.772	-0.048	0.0277
	CLss/F (L/hr)	31	α	-1.024	-2.514	0.466	-2.817	0.769	0.2524
			β	0.479	0.133	0.825	0.063	0.895	0.0255

Note: [1]PK parameter Cmax, AUC0-last, AUC0-inf, AUCtau are dose normalized, CL/F, Vd/F and CLr are not dose-normalized.
[2] The power model is log(Y) = α + βlog(X), Y are the PK parameters from different renal function cohorts. X are creatinine clearances from different renal function cohorts.

Source: Table 14.4.4.2.1, Clinical Study Report No. TAS-102-107 (pages 191)

Per the clinical pharmacology review of the original NDA (DARRTS date: 08/21/2015), the E-R relationship for efficacy and safety could not be adequately characterized as only 26% (138/534) patients in the TAS-102 treatment arm of the registration trial Study RECOURSE (TPU-TAS-102-301) had evaluable PK data. The median overall survival (OS) rate appeared more favorable in the subpopulation with higher trifluridine AUCs compared to the subpopulation with lower trifluridine AUCs (9.2 vs. 8.1 months). The incidence of Grade ≥3 neutropenia and any Grade ≥3

drug related AEs appear higher (>10%) in the group with higher trifluridine AUC compared with the group with lower trifluridine AUC. The rate of any dose reduction was also higher in the group with higher trifluridine AUC group (23%) compared with the group with lower trifluridine AUC group (9%). Therefore, achieving similar steady-state AUC of FTD is essential to ensure efficacious and acceptable safety for RI patients.

In patients with mild RI, the steady-state AUC of FTD was comparable to that of patients with normal renal function with a GMR ratio of 0.99. Hence, no dose adjustment is needed for mild RI patients.

In patients with moderate RI, the steady-state AUC of FTD was higher than that of patients with normal renal function with a GMR ratio of 1.56. In the pivotal phase III efficacy and safety trial RECOURSE, same dose of Lonsurf resulted in a 43% higher steady-state AUC of FTD in patients with moderate RI, and no dose adjustment was recommended for moderate RI patients in the approved label. In addition, the safety results showed comparable incidence rates between the mild and moderate RI cohorts administered with the same dose (35 mg/m^2) in terms of Grade 3 and higher AEs and SAEs. Therefore, the reviewer agrees to continue recommending no dose adjustment for patients with moderate RI.

Severe RI resulted in a 2.4-fold increase in steady-state dose-normalized AUC of FTD compared to patients with normal renal function. If matching the exposure, the dose should be adjusted to 35/2.4 = ~ 15 mg/m^2. Taiho stated that the steady-state AUC of FTD tended to increase more than proportional in the dose range of 15 to 35 mg/m^2. The CL/F and apparent volume of distribution (Vd/F) of FTD generally remained constant at the dose range of 20 to 35 mg/m^2. Therefore, dose level of 15 mg/m^2 may cause underexposure of FTD, then affect efficacy. Hence, Taiho proposed a dose adjustment to 20 mg/m^2 for patients with severe RI. From a safety perspective, dose adjustment to 20 mg/m^2 for the patients with severe RI showed lower incidence rates of Grade 3 and higher AEs and SAEs compared to patients with mild and moderate RI dosed at 35 mg/m^2, and comparable to patients with normal renal function group. The reviewer agrees with Taiho's proposal of adjusting starting dose of Lonsurf to 20 mg/m^2 (BID) for patients with severe RI.

4.5 SAFETY RESULTS

The safety results of study TAS-102-107 were summarized in Table 11 below. Grade 3 or higher adverse events (AEs) (e.g. anemia, neutrophil count decreased, and neutropenia etc.) showed higher incidence in the mild (83.3%) and moderate (90.9%) RI cohorts compared to the normal renal function cohort (50.0%). However, the incidence of Grade 3 or higher AEs in patients with severe RI (75.0%) who received 20 mg/m^2/dose did not show an increase in the AE incidence when compared to the mild or moderate RI cohort. Similar trend was also observed for serious adverse events (SAEs). The incidence of SAEs was higher in the mild (58.3%) and moderate (45.5%) RI cohorts compared to the normal renal function cohort (33.3%). However, patients with severe RI (37.5%) who received 20 mg/m^2/dose did not show a meaningful increase in the SAE incidence compared to the normal renal function cohort (33.3%). No AEs with the outcome of death were reported. The most frequently reported AEs were consistent with the known safety profile of TAS-102. For all patients in the As-treated Population the most frequently reported preferred terms (≥ 25%) were fatigue (55.8%), nausea (48.8%), decreased appetite (48.8%),

anemia (39.5%), vomiting (34.9%), dehydration (27.9%), diarrhea (25.6%), and dyspnea (25.6%).

Table 11. Summary of Adverse Events (As-treated Population)

Patients with:	Normal Cohort (N=12)	Mild Renal Impairment Cohort (N=12)	Moderate Renal Impairment Cohort (N=11)	Severe Renal Impairment Cohort (N=8)	Overall (N=43)
Adverse events	12 (100%)	12 (100%)	11 (100%)	8 (100%)	43 (100%)
Serious adverse events	4 (33.3%)	7 (58.3%)	5 (45.5%)	3 (37.5%)	19 (44.2%)
Grade 3 or higher AEs	6 (50.0%)	10 (83.3%)	10 (90.9%)	6 (75.0%)	32 (74.4%)
Treatment-related AEs	10 (83.3%)	10 (83.3%)	11 (100%)	6 (75.0%)	37 (86.0%)
Adverse events leading to treatment discontinuation	1 (8.3%)	3 (25.0%)	2 (18.2%)	1 (12.5%)	7 (16.3%)
Adverse events with outcome of death	0	0	0	0	0
Cycle 1					
Adverse events	12 (100%)	12 (100%)	9 (81.8%)	6 (75.0%)	39 (90.7%)
Serious adverse events	1 (8.3%)	3 (25.0%)	2 (18.2%)	1 (12.5%)	7 (16.3%)
Grade 3 or higher AEs	2 (16.7%)	3 (25.0%)	5 (45.5%)	3 (37.5%)	13 (30.2%)
Treatment-related AEs	9 (75.0%)	9 (75.0%)	9 (81.8%)	5 (62.5%)	32 (74.4%)
Adverse events leading to treatment discontinuation	0	0	0	0	0
Adverse events with outcome of death	0	0	0	0	0

AE = adverse event
Note: Percentages are based on number of patients in the As-treated Population within the same cohort.
Source: Table 21, Clinical Study Report No. TAS-102-107 (pages 87)

In conclusion, the safety findings in patients with mild and moderate RI were consistent with the currently known safety profile in this population. Patients with severe RI who received 20 mg/m^2/dose did not show a meaningful difference in safety profiles compared to the normal renal function and mild RI cohorts. Therefore, a dose of TAS-102 at 20 mg/m^2 BID is appropriate and tolerable for patients with severe RI.

5 PROPOSED LABELING

Taiho proposed to modify sections 8.6 and 12.3 in orange underlined text. The blue underline and strikethrough text identify FDA proposed the following modifications to the Taiho's proposed labeling changes. Taiho accepted all the edits provided by the FDA on 12/6/2019.

2.3 Recommended Dosage for Renal Impairment

Severe Renal Impairment

In patients with severe renal impairment [creatinine clearance (CLcr) of 15 to 29 mL/min as determined by the Cockcroft-Gault formula], the recommended dosage is 20 mg/m^2 (based on the trifluridine component) oral twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle (Table 2) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Reduce dose to 15 mg/m^2 twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily (Table 2). Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 15 mg/m2 twice daily.

Table 2 Recommended Dosage for Severe Renal Impairment According to BSA

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15mg	20mg
For a dose of 20 mg/m^2 twice daily:				
< 1.14	40	20	0	1
1.14 – 1.34	50	25*	2 in the evening*	1 in the morning*
1.35 – 1.59	60	30	2	0
1.60 – 1.94	70	35	1	1
1.95 – 2.09	80	40	0	2
2.10 – 2.34	90	45	3	0
≥ 2.35	100	50	2	1
For a dose of 15 mg/m^2 twice daily:				
< 1.15	30	15	1	0
1.15 – 1.49	40	20	0	1
1.50 – 1.84	50	25*	2 in the evening*	1 in the morning*
1.85 – 2.09	60	30	2	0
2.10 – 2.34	70	35	1	1
≥ 2.35	80	40	0	2

* For a total daily dose of 50 mg, instruct patients to take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

8.6 RI

12.3 Pharmacokinetics

Patients with Renal Impairment

~~In RECOURSE, using the Cockcroft-Gault formula for creatinine clearance, the estimated mean AUC of trifluridine at steady state was 31% higher in patients with mild renal impairment (CLcr~~

~~= 60 to 89 mL/min) and 43% higher in patients with moderate renal impairment (CLcr = 30 to 59 mL/min) than that in patient with normal renal function (CLcr ≥ 90 mL/min). The estimated mean AUC of tipiracil was 34% higher in patients with mild RI and 65% higher in patients with moderate renal impairment than that in patients with normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease [see Use in Specific Populations (b) (4)].~~

(b) (4)

SIGNATURES:

Yibo Wang, Ph.D. Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V

Cc: OOD DO2: RPM – G Davis; MO – L Marcus; MTL – M Donoghue
DCPV: DDD – B Booth; DD – NA Rahman

6 APPENDIX

Summary method performance of a bioanalytical method to measure FTD, FTY, and TPI in human plasma and urine

Bioanalytical method validation report name, amendments, and hyperlinks	1. Analytical method validation for the determination of FTD and FTY in human plasma and urine by liquid chromatography with tandem mass spectrometry, Study No. P04-10402, (b) (4) July 2005. 2. Analytical method validation for the determination of TPI in human plasma and urine by liquid chromatography with tandem mass spectrometry, Study No. P04-10403, (b) (4) July 2005. 3. Partial validation for determination of FTD, FTY, and TPI in human plasma and urine by liquid chromatography with tandem mass spectrometry, Study No. P13-10422, (b) (4) October 2013. 4. Additional study of analytical method validation for the determination of FTD, FTY, and TPI in human plasma and urine by liquid chromatography with tandem mass spectrometry, Study No. P12-10413, (b) (4) September 2012. 5. Additional study of long-term stability of FTD, FTY, and TPI in human plasma and urine, Study No. P12-10414, (b) (4) October 2013. 6. Partial validation for determination of FTD, FTY, and TPI in human plasma and urine by liquid chromatography with tandem mass spectrometry (replacement of autosampler), Study No. P14-10427, (b) (4) August 2015.
Method description	Liquid chromatography with tandem mass spectrometry
Materials used for calibration curve & concentration	**Plasma**: Matrix: Human plasma Sex: Male and female Supplier: (b) (4) Anticoagulant: Sodium heparin Concentrations: FTD and FTY: 5.00, 10.0, 25.0, 50.0, 200, 500, 2500, and 5000 ng/mL TPI: 0.200, 0.400, 1.00, 2.00, 5.00, 20.0, 100, and 200 ng/mL **Urine**: Matrix: Human urine Sex: Male and female Concentrations: FTD and FTY: 0.200, 0.400, 1.00, 2.00, 5.00, 20.0, 50.0, 100, and 200 µg/mL TPI: 0.200, 0.400, 1.00, 2.00, 5.00, 20.0, 50.0, and 100 µg/mL
Validated assay range	**Plasma**: FTD and FTY: 5.00 to 5000 ng/mL TPI: 0.200 to 200 ng/mL **Urine**: FTD and FTY: 0.200 to 200 µg/mL TPI: 0.200 to 100 µg/mL
Material used for QCs & concentration	**Plasma**: Matrix: Human plasma Sex: Male and female Supplier: (b) (4) Anticoagulant: Sodium heparin Concentrations:

	FTD and FTY: 5.00, 10.0, 250, and 4000 ng/mL TPI: 0.200, 0.400, 10.0, and 160 ng/mL **Urine**: Matrix: Human urine Sex: Male and female Concentrations: FTD and FTY: 0.200, 0.400, 25.0, and 160 µg/mL TPI: 0.200, 0.400, 10.0, and 80.0 µg/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Calibration curve model $y = ax + b$, weighted least-squares linear regression y Peak area ratio (peak area of FTD/peak area of $^{13}C,^{15}N_2$-FTD) (peak area of FTY/peak area of $^{13}C,^{15}N_2$-FTY) (peak area of TPI/peak area of $^{13}C,^{15}N_2$-TPI) x Nominal concentration a Slope b y-Intercept r Correlation coefficient Weighting factor $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	**Plasma**: 8 (FTD, FTY, and TPI) **Urine**: 9 (FTD and FTY), 8 (TPI)	P04-10402 P04-10403
	Cumulative accuracy (%bias) from LLOQ to ULOQ	**Plasma**: FTD: -3.4 to 2.7% FTY: -8.8 to 8.0% TPI: -2.3 to 2.7% **Urine**: FTD: -5.0 to 9.6% FTY: -5.0 to 6.3% TPI: -4.0 to 2.0%	P04-10402 P04-10403
	Cumulative precision (%CV) from LLOQ to ULOQ	**Plasma**: **FTD: ≤ 3.5%** **FTY: ≤ 6.5%** **TPI: ≤ 4.6%** **Urine**: **FTD: ≤ 4.2%** **FTY: ≤ 4.2%** **TPI: ≤ 4.7%**	P04-10402 P04-10403
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs:	**Plasma**: FTD: -4.0 to 2.4% FTY: -7.7 to 6.0% TPI: 1.0 to 4.0% **Urine**:	P04-10402 P04-10403

		FTD: -0.4 to 5.5% FTY: -2.5 to 2.8% TPI: 2.0 to 5.9%	
	Inter-batch %CV QCs:	**Plasma**: **FTD**: ≤ 6.7% **FTY**: ≤ 10.7% **TPI**: ≤ 9.6% **Urine**: **FTD**: ≤ 9.5% **FTY**: ≤ 6.8% **TPI**: ≤ 5.2%	P04-10402 P04-10403
	Total error QCs:	Not applicable	Not applicable
Selectivity & matrix effect	No interfering peaks were found in individual blank samples. FTD, FTY, and TPI were not affected by presence of endogenous substances in human plasma and urine.		P04-10402 P04-10403 P12-10413
Interference & specificity	The concomitant drug (FTD, FTY, TPI, irinotecan, and SN-38) did not affect the determination of FTD, FTY, or TPI.		P13-10422
Hemolysis effect	Not applicable		Not applicable
Lipemic effect	Not applicable		Not applicable
Dilution linearity & hook effect	Not applicable		Not applicable
Bench-top/process stability	FTD, FTY, and TPI (plasma and urine): Room temperature, 24 hours		P04-10402 P04-10403
Freeze-Thaw stability	FTD, FTY, and TPI (plasma and urine): 6 cycles		P04-10402 P04-10403
Long-term storage	–30°C to –15°C: FTD and FTY (plasma): 370 days; FTD and FTY (urine): 415 days; and TPI (plasma and urine): 366 days –65°C or below: FTD and FTY (plasma): 362 days; FTD (urine): 373 days; FTY (urine): 189 days; TPI (plasma): 370 days; and TPI (urine): 369 days		P04-10405 P12-10414 P14-10426
Parallelism	Not applicable		Not applicable
Carry over	No carry-over peaks of FTD, FTY, TPI, and the corresponding ISs were observed on the MRM chromatograms of the blank samples.		P04-10402 P04-10403
Method performance in study TAS-102-107 Determination of FTD, FTY, and TPI Concentrations in Human Plasma and Urine in "A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAS-102 in Patients with Advanced Solid Tumors and Varying Degrees of Renal Impairment", Study No. P 14-10426, (b) (4) March 2019.			
Assay passing rate	(including incurred sample reanalysis (ISR)) 100%		P14-10426

Standard curve performance	**Plasma**: Cumulative bias range: FTD: -1.1 to 1.5% FTY: -1.4 to 2.1% TPI: -3.4 to 2.1% Cumulative precision: **FTD**: ≤ 4.1% **FTY**: ≤ 4.9% **TPI**: ≤ 6.6% **Urine**: Cumulative bias range: FTD: -4.4 to 3.7% FTY: -6.3 to 2.5% TPI: -1.4 to 1.0% Cumulative precision: **FTD**: ≤ 4.7% **FTY**: ≤ 6.6% **TPI**: ≤ 2.8%	P14-10426
QC performance	**Plasma**: Cumulative bias range: FTD: 1.0 to 4.3% FTY: 0.8 to 6.0% TPI: 1.0 to 1.9% Cumulative precision **FTD**: ≤ 5.6% **FTY**: ≤ 10.0% **TPI**: ≤ 10.8% TE: Not applicable **Urine**: Cumulative bias range: FTD: -2.8 to 1.9% FTY: -2.7 to 4.6% TPI: -0.1 to 1.2% Cumulative precision: **FTD**: ≤ 5.6% **FTY**: ≤ 9.2% **TPI**: ≤ 4.7% TE: Not applicable	P14-10426
Method reproducibility	Incurred sample reanalysis was performed in 10.0% (FTD, FTY, and TPI) of study samples and 89.3% (FTD), 90.7% (FTY), and 100% (TPI) of samples met the pre-specified criteria.	P14-10426
Study sample analysis/ stability	FTD, FTY, $^{13}C,^{15}N_2$-FTD, and $^{13}C,^{15}N_2$-FTY (stock and working solutions): Up to 41 days after preparation protected from light at 1°C to 10°C, airtight TPI and $^{13}C,^{15}N_2$-TPI (working solution): Up to 34 days after preparation protected from light at 1°C to 10°C, airtight **Plasma** FTD and FTY: Up to 370 days after plasma preparation (–30°C to –15°C) 6 freeze (–30°C to –15°C)-thaw (room temperature) cycles	
	TPI: Up to 366 days after plasma preparation (–30°C to –15°C) 6 freeze (–30°C to –15°C)-thaw (room temperature) cycles **Urine** FTD and FTY: Up to 415 days after urine preparation (–30°C to –15°C) 6 freeze (–30°C to –15°C)-thaw (room temperature) cycles TPI: Up to 366 days after urine preparation (–30°C to –15°C) 6 freeze (–30°C to –15°C)-thaw (room temperature) cycles	

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/s/

YI-BO WANG
12/19/2019 12:28:50 PM

HONG ZHAO
12/19/2019 12:30:15 PM
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 29, 2019

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: sNDA 207981/009BLA 761034/021– Taiho Oncology, Inc. Genentech, Inc.– Lonsurf (trifluridine and tipiracil) FDA request for additional information – Labeling Proposal

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Dear Mr. Palm,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lonsurf (trifluridine and tipiracil), tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil.

Please also refer to your June 24, 2019, supplemental application requesting to update the Use in Specific Populations, Renal Impairment, subsection (8.6) and the Clinical Pharmacology, Pharmacokinetics, subsection (12.3) of the package insert to fulfill postmarketing requirement (PMR) PMR 2963-2.

Currently, your submission is under review and we have attached our proposal to the package insert. Please review our comments/proposed edits and provide feedback.

Please provide a response by close of business Tuesday, November 5, 2019. Should you have any additional comments or concerns, please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

22 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GINA M DAVIS
10/29/2019 12:40:55 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 17, 2019

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: sNDA 207981/009; Labeling Supplement –Taiho Oncology, Inc. Lonsurf - FDA request for information

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Dear Mr. Palm:

Please refer to your Supplemental New Drug Application (sNDA) dated June 24, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lonsurf (trifluridine and tipiracil), tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil.

Currently your submission is under review and we have the following comments and requests for information.

1. **Clarify** if the assays used to measure the concentrations of FTD, FTY, and TPI in plasma and urine for the dedicated renal impairment study (TAS-102-107) is the same as those used in the original submission.
2. **Submit** the bioanalytical report for study (TAS-102-107).

3. **Complete** the bioanalytical method performance summary table below for the LC-MS/MS method and its performance in study (TAS-102-107). Do not delete any rows or columns from the tables. State "not applicable" if certain rows or columns are not applicable. Include any additional bioanalytical data that may be relevant to the submission.

Table 1. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks	
Method description	
Materials used for calibration curve & concentration	
Validated assay range	
Material used for QCs & concentration	
Minimum required dilutions (MRDs)	

Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	
	Cumulative accuracy (%bias) from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs:	x to y%	
	Inter-batch %CV QCs:	≤ x%	
	Total error QCs:	≤ x%	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		
Dilution linearity & hook effect	Describe data here		
Bench-top/process stability	Describe data here		
Freeze-Thaw stability	Describe data here		
Long-term storage	Describe data here		
Parallelism	Describe data here		
Carry over	Describe data here		
Method performance in study TAS-102-107 (In addition to the report name, also provide hyperlink to the report)			
Assay passing rate	(including incurred sample reanalysis (ISR))		
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV		
QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)		
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria		

Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples

Please provide a response by close of business Wednesday, October 23, 2019, or sooner.

Should you have any questions or concerns.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/17/2019 06:04:44 PM

NDA 207981/S-009

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Taiho Oncology, Inc.
Attention: Alpesh Patel
Director, Regulatory Affairs
101 Carnegie Center, Suite 101
Princeton, NJ 08540

Dear Mr. Patel:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 207981

SUPPLEMENT NUMBER: 009

PRODUCT NAME: Lonsurf (trifluridine and tipiracil), tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil

DATE OF SUBMISSION: June 24, 2019

DATE OF RECEIPT: June 24, 2019

This supplemental application proposes to update the Use in Specific Populations, Renal Impairment, subsection (8.6) and the Clinical Pharmacology, Pharmacokinetics, subsection (12.3) of the package insert to fulfill postmarketing requirement (PMR) PMR 2963-2.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 23, 2019, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be December 24, 2019.

If you have questions, call Gina Davis, Senior Regulatory Health Project Manager at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
08/02/2019 12:25:03 PM